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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,422	11/07/2006	Eggert Stockfleth	50125/084002	7550

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EXAMINER	
MI, QIUWEN	
ART UNIT	PAPER NUMBER
1655	

NOTIFICATION DATE	DELIVERY MODE
06/29/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/574,422	STOCKFLETH, EGGERT	
	Examiner	Art Unit	
	QIUWEN MI	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 8-36* is/are pending in the application.

4a) Of the above claim(s) *33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6, 8-32, 35, and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATIONS

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/2/09 has been entered.

Claims 2 and 7 have been cancelled. Claims 1, 3-6, and 8-36 are pending. Claims 33 and 34 are withdrawn from consideration. **Claims 1, 3-6, 8-32, 35, and 36 are examined on the merits.**

Any rejection that is not reiterated is hereby withdrawn.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 8-32, and 36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8, 16, 18, 23-27,

and 30-33 of copending Application No. 10/682, 612. Although the conflicting claims are not identical, they are not patentably distinct from each other because actinic keratosis in case 10/682,612 is a species of the broad genus "pre-cancerous lesions" in the instant case, thus claims 1-6, 8, 16, 18, 23-27, and 30-33 of copending Application No. 10/682, 612 'anticipate' the Claims 1, 6, 8-32, and 36 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections –35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5, and 8-20 are rejected under 35 USC § 102 (b) as being anticipated by Yanaga et al (Yanaga et al, Prevention of carcinogenesis of mouse mammary epithelial cells RIII/MG by epigallocatechin gallate, International journal of molecular medicine 10: 311-315, 2002), as evidenced by Dou et al (US 2002/0151582)*.

Yanaga et al teach "The chemopreventive effect of the polyphenols abundant in green tea on carcinogenesis has been attracting attention in recent years. Among tea polyphenols, epigallocatechin gallate (EGCG) has been studied as a preventive substance for carcinogenesis.

We investigated the chemopreventive effect in a group treated with EGCG in vitro and in vivo using mouse mammary epithelial cells RIII/MG (thus skin lesion) (thus non-virally induced lesion, not caused by papilloma virus, not a lesion selected from the group consisting of phyperplasia, Condyloma acuminata, warts and cervical intra-epithelial neoplasia). In the in vitro experiment, crude catechin (catechin) containing 50% or more EGCG significantly inhibited the growth of RIII/MG cells, which were precancerous cultured cells. Many cells died, and a DNA ladder was observed. In the in vivo experiment, RIII/MG cells formed a tumor after 13 weeks in a group without catechin treatment, and the tumor formation rate in the 20th week was 40%. In a group treated with 0.1% catechin, a tumor began to grow in the 13^{th} week, and the tumor formation rate in the 20th week was 20%. In a group treated with 1% catechin, no tumor was detected even in the 20th week. Yanaga et al teach in mice not given catechin, a tumor formed in 25-30% of animals in the 18-20 th week after transplanation of precancerous RIII/MG cells. The tumors that formed were histopatholigically cancerous, suggesting that the precancerous cells grew subcutaneously in nude mice and developed into cancer cells during the formation of the phyma. In contrast, tumor formation was inhibited in mice treated with catechin in a concentration dependent manner. No tumor was formed in the group treated with a high concentration of catechin. There was no significant difference in the change in body weight between the catechin treatment groups and the non-treatment group during the observation period. Tissue samples were stained by the nick-end-labeling method and apoptosis was observed in many cells. Based on the above findings, EGCG inhibited growth in the mouse viral mammary epithelial carcinogenesis model RIII/MG, and induced apoptosis, suggesting a clinical usefulness of EGCG as a chemopreventive substance" (see Abstract). Yanaga et al also teach

"this study showed that EGCG inhibited the growth and induced apoptosis in precancerous mammary RIII/MG cells in vivo, as observed in vitro" (page 314, 1st column, last paragraph).

As evidenced by Dou et al, green tea contains polyphenol compounds EGCG (formula I and II in claims 13 and 14 are thus met), ECG, GCG, or CG (claim 3).

Therefore, the reference is deemed to anticipate the instant claim above.

Claim Rejections –35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, and 8-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanaga et al (Yanaga et al, Prevention of carcinogenesis of mouse mammary epithelial cells RIII/MG by epigallocatechin gallate, International journal of molecular medicine 10: 311-315, 2002), as evidenced by Dou et al (US 2002/0151582)*.

Yanaga et al teach "The chemopreventive effect of the polyphenols abundant in green tea on carcinogenesis has been attracting attention in recent years. Among tea polyphenols, epigallocatechin gallate (EGCG) has been studied as a preventive substance for carcinogenesis. We investigated the chemopreventive effect in a group treated with EGCG in vitro and in vivo using mouse mammary epithelial cells RIII/MG (thus skin lesion) (thus non-virally induced lesion, not caused by papilloma virus, not a lesion selected from the group consisting of phyperplasia, Condyloma acuminata, warts and cervical intra-epithelial neoplasia). In the in

vitro experiment, crude catechin (catechin) containing 50% or more EGCG significantly inhibited the growth of RIII/MG cells, which were precancerous cultured cells. Many cells died, and a DNA ladder was observed. In the in vivo experiment, RIII/MG cells formed a tumor after 13 weeks in a group without catechin treatment, and the tumor formation rate in the 20th week was 40%. In a group treated with 0.1% catechin, a tumor began to grow in the 13th week, and the tumor formation rate in the 20th week was 20%. In a group treated with 1% catechin, no tumor was detected even in the 20th week. Yanaga et al teach in mice not given catechin, a tumor formed in 25-30% of animals in the 18-20 th week after transplanation of precancerous RIII/MG cells. The tumors that formed were histopatholigically cancerous, suggesting that the precancerous cells grew subcutaneously in nude mice and developed into cancer cells during the formation of the phyma. In contrast, tumor formation was inhibited in mice treated with catechin in a concentration dependent manner. No tumor was formed in the group treated with a high concentration of catechin. There was no significant difference in the change in body weight between the catechin treatment groups and the non-treatment group during the observation period. Tissue samples were stained by the nick-end-labeling method and apoptosis was observed in many cells. Based on the above findings, EGCG inhibited growth in the mouse viral mammary epithelial carcinogenesis model RIII/MG, and induced apoptosis, suggesting a clinical usefulness of EGCG as a chemopreventive substance" (see Abstract). Yanaga et al also teach "this study showed that EGCG inhibited the growth and induced apoptosis in precancerous mammary RIII/MG cells in vivo, as observed in vitro" (page 314, 1st column, last paragraph).

As evidenced by Dou et al (US 2002/0151582), green tea contains polyphenol compounds EGCG (formula I and II in claims 13 and 14 are thus met), ECG, GCG, or CG (claim 3).

Yanaga et al do not teach the claimed amounts of the polyphenols in the composition.

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use the inventions of Yanaga et al since they provide scientific data for green tea extract on chemoprevention of precancerous cells, one of ordinary skill in the art would have been motivated to make the modifications. The result-effective adjustment in conventional working parameters (e.g., determining an appropriate amount of the each polyphenol components as claimed isolated from green tea within the composition) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. The differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum

combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). see MPEP § 2144.05 part II A. Although the prior art did not specifically disclose the amounts of each catechin constituent, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal concentrations of components because concentrations of the claimed components are art-recognized result effective variables because they have the ability to prevent of carcinogenesis of mouse mammary precancerous cells, which would have been routinely determined and optimized in the pharmaceutical art.

Since the mouse mammary epithelial cells RIII/MG is non-virally induced lesion, not caused by papilloma virus, not a lesion selected from the group consisting of phyperplasia, Condyloma acuminata, warts and cervical intra-epithelial neoplasia, thus the limitation of claims 3-5 is met.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Claims 1, 3-6, 8-32, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanaga et al and Dou et al as applied to claims 1, 3-5, and 8-26 above, and further in view of Brash et al (US 2002/0198161), and further in view of Voet (US 6,723,750).

The teachings of Yanaga et al and Dou et al are set forth above and applied as before.

The combination of Yanaga et al and Dou et al do not specifically teach topical application of green tea extract, additive isopropyl myristate, form of ointment, or combined with different treatment curettage, or the claimed amount of the polyphenols.

Brash et al teaches that skin precancers are being treated, the preferred mode of administration is topical. The topical application may contain carrier, excipient or vehicle ingredients such as isopropyl myristate etc., and mixtures thereof to form lotions, creams, emulsions, gels, or ointments [0086]. Brash et al also teaches a method of preventing a precancer, cancer, hyperproliferative or benign dysproliferative disorder in a human subject (claim 76).

Voet teaches that the current management options for visible or easily perceived and diagnosed precancerous dermatological lesions such as Aks (thus claim 35 is met) include cryosurgery with liquid nitrogen, topical treatment, and curettage (col 2, lines 15-20). Voet also teaches that curettage, which involves the use of a curette to scrape away the lesion, is another common method of treatment for easily perceptible precancerous skin lesions. The primary advantage of curettage is the ability to submit the specimen for histologic analysis.

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use the carrier isopropyl myristate and ointment form for

human subject from Brash et al, and the treatment of curettage from Voet in the current invention since carrier isopropyl myristate and ointment form are the conventional carrier and pharmaceutical form that have been used successfully in treating precancerous lesions in the topical route according to Brash et al; and combining the treatment curettage from Voet with the topical could monitor the histologic status of the tissue treated by topical administration. Since both Brash et al, and the treatment of curettage from Voet yielded beneficial results in treating precancerous lesions, one of ordinary skill in the art would have been motivated to make the modifications to combine the references together.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Claims 1, 3-6, 8-20, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanaga et al and Dou et al as applied to claims 1, 3-5, and 8-20 above, and further in view of An Kathy et al (Cyclooxygenase-2 expression in murine and human nonmelanoma skin cancers: implications for therapeutic approaches, Photochemistry and photobiology, (2002 Jul) Vol. 76, No. 1, pp. 73-80).

The teachings of Yanaga et al and Dou et al are set forth above and applied as before.

The combination of Yanaga et al and Dou et al do not specifically teach treating actinic keratosis.

An Kathy et al teach COX-2 expression was also increased in human actinic keratoses. An Kathy et al also teach acute exposure of the human skin to UVB (minimum erythema dose x 4) caused a transient enhancement of the COX-2 expression, which reverted to baseline within hours; however, in murine skin the expression persisted for several days. Pretreatment with the topically applied green tea extract (1 mg/cm2) largely abrogated the acute COX-2 response to UVB in mice or humans. In summary, enhanced COX-2 expression serves as a marker of epidermal UVB exposure for murine and human NMSC. These results suggest that COX-2 inhibitors could have potent anticarcinogenic effects in UVB-induced skin cancer (see Abstract).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use the green tea extract to treat actinic keratoses from An Kathy et al since An Kathy et al teach green tea extract (1 mg/cm2) largely abrogated the acute COX-2 response to UVB in mice or humans. Since both Yanaga et al and An Kathy et al teach using green tea extract to treat precancerous lesion, one of ordinary skill in the art would have been motivated to make the modifications and combine the two references together.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

*This reference is cited merely to relay an intrinsic property and is not used in the basis for rejection *per se*.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Qiuwen Mi whose telephone number is 571-272-5984. The examiner can normally be reached on 8 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Qiuwen Mi/

Examiner, Art Unit 1655